

Sleep Related Eating Disorder as an Unexpected Effect of Zolpidem

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Abstract

Zolpidem is a sedative-hypnotic drug used to treat in sleep disorders, and it is the most commonly prescribed drug for insomnia. It reduces sleep latency and increases total sleep time. However, some studies have reported that zolpidem might induce sleep related eating disorder (SRED). SRED is characterized by recurrent episodes of compulsive and involuntary eating during night sleep, accompanied by partial consciousness and limited subsequent recall. The pathophysiology of SRED is unknown. Patients with SRED usually suffer from other sleep disorders such as sleepwalking, restless legs syndrome, and obstructive sleep apnea. In this article, we present an overview of case reports on SRED induced by zolpidem.

Keywords

Zolpidem, Sleep Related Eating Disorder, Insomnia

1. Introduction

Insomnia is a very common condition worldwide. Many patients with insomnia have only transient difficulties in falling asleep or staying awake, which resolve in a few days. However, approximately 20% of insomnia patients suffer from chronic insomnia [1]. Chronic insomnia impairs quality of life and reduces the ability to perform daily activities. Short-term treatments with benzodiazepine or non-benzodiazepine hypnotics are used to treat chronic insomnia [2]. Zolpidem¹ is a non-benzodiazepine receptor agonist, and a highly effective hypnotic with a short half-life [3]. Compared with other hypnotics, zolpidem induces a pattern of sleep that is more similar to natural sleep. Several clinical trials that have evaluated zolpidem in the treatment of chronic insomnia have shown that the med-

¹Zolpidem induced SRED.

iation is well tolerated and remains effective for up to 12 months without any evidence of significant tolerance or rebound insomnia on discontinuation [3] [4]. In addition, zolpidem appears to have low abuse liability at doses commonly used to treat insomnia. Therefore, owing to these several clinical advantages, zolpidem is widely prescribed for treating insomnia.

However, some studies have reported that zolpidem is associated with sleep-related eating disorder (SRED) as well as sleepwalking [4]. According to the International Classification of Sleep Disorders, Second Edition [5], SRED is classified as parasomnia and is characterized by recurrent episodes of involuntary eating and drinking in the middle of sleep periods with problematic consequences. Patients have reported involuntary eating and their cohabitants find them to have difficulty in remaining to fully awake. This behavior may lead to morning bloating, social embarrassment, and weight gain. SRED is also associated with sleep disturbance, which can cause fatigue, somnolence, poor cognitive performance, irritability, and obesity [6]. The exact etiology of SRED is not clear [7]. It is often associated with other sleep disorders such as restless legs syndrome (RLS) and obstructive sleep apnea (OSA) [8]. In addition, SRED has been reported to be associated with and triggered by the use of psychotropic medications such as tricyclic antidepressants anticholinergics, olanzapine, and risperidone [9]. Recently, SRED has been implicated with the use of zolpidem [10]. The chemical structure of zolpidem is different from those of benzodiazepines, barbiturates, and other hypnotic drugs, and hence may be related to the development of SRED. Sporadic cases of zolpidem-induced SRED have been reported in the literature, and we recently experienced a case of zolpidem-induced SRED in a patient with attention-deficit hyperactivity disorder (unpublished data).

Therefore, we aimed to provide an overview of patients with SRED induced by zolpidem.

2. Methods

Electronic databases were searched through the academic search engine, MEDLINE. The following headings and keywords were used: 1) “zolpidem”, 2) “sleep related eating disorder” or “SRED”, and 3) “case” or “case report”. The search sets included all papers published from January 2000 to January 2019. This search was limited to studies written in English. The search produced 19 articles. All the papers were then manually reviewed to ensure that the studies investigated SRED induced by zolpidem. Review articles were excluded. A total of 10 studies met the criteria for inclusion to the present study. **Figure 1** shows the initial identification of 19 studies and the process through which the final 10 studies were selected for inclusion.

3. Result

3.1. Overview of the Reviewed Studies

A total of 10 case reports met the criteria for inclusion to this review. **Table 1** provides

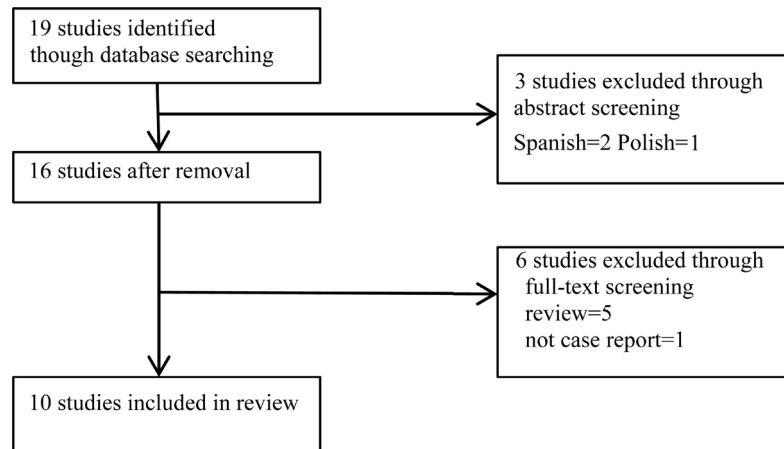


Figure 1. Flow chart for identifying studies.

Table 1. Summary of reviewed case reports.

Author	Age of onset	Gender	Recall of nocturnal eating	Zolpidem (mg)	Associated sleep disorders
Park Y.M. <i>et al.</i> [8]	71	male	amnesic	12.5	OSA, RLS
Kim H.K.E. <i>et al.</i> [19]	57	female	full recall	10	RLS
Nzwalo <i>et al.</i> [18]	53	female	amnesic	10	none
Wing Y.K. <i>et al.</i> [17]	61	female	NA	10	OSA
	64	male	NA	10	OSA
	63	male	NA	10	OSA
	54	female	NA	10	none
	56	female	NA	10	narcolepsy
	44	female	NA	10	none
	29	female	NA	10	OSA
Hoque R., Chesson A.L. [16]	28	male	amnesic	10	OSA
	51	female	amnesic	10	OSA
Yun C.H., Ji K.H. [15]	45	male	amnesic	10	RLS
Dang A. <i>et al.</i> [14]	45	male	amnesic	10	none
Chiang A., Krystal A. [13]	75	female	amnesic	10 - 12.5	OSA
	70	female	amnesic	10 - 12.5	RLS, mild OSA
Najjar M. <i>et al.</i> [12]	46	female	amnesic - partial recall	6.25	mild OSA
Morgenthaler T.I., Silber M.H. [11]	51	female	amnesic	10	RLS
	65	male	some recall - amnesic	10 - 20	RLS, OSA, sleep walking
	41	male	amnesic	15 - 30	RLS, OSA
	64	male	full recall	5 - 10	RLS, OSA
	56	female	amnesic	10	RLS, sleep walking

NA: Information not available; OSA: obstructive sleep apnea; RLS: restless leg syndrome.

an overview of the reviewed articles. We found 22 cases of zolpidem-induced SRED. The average age of the patients was 54.0 years old (range 28 years to 71 years). Thirteen patients were female, 59.1%; 13/22 of cases. Zolpidem was prescribed for insomnia in all cases. In 22 cases, there were 13 (59.1%) subjects were OSA, 9 (41.0%) subjects were RLS, and 2 (9.1%) subjects were sleep walking. Discontinuation of zolpidem led to remission of SRED in all cases.

3.2. Details of Each Case

Morgenthaler *et al.* [11] reported five cases (two females) of zolpidem induced SRED who were middle aged and had RLS. Two of these five patients had intermittent episodes of conscious nocturnal eating. Each patient began amnesic night eating, which stopped with discontinuation of zolpidem.

Najjar [12] reported the case of a 46-year-old woman who developed SRED after 3 weeks of taking 6.25 mg of zolpidem. The patient had total amnesia or partial recall of night eating. After zolpidem was discontinued, nocturnal eating stopped completely.

Chiang *et al.* [13] reported two cases. The first was a 75-year-old woman with RLS and mild OSA. As soon as the patient was switched from zolpidem 10 mg to 12.5 mg of extended-release (ER) zolpidem, she developed amnesic SRED. After she stopped taking the ER zolpidem and resumed her usual zolpidem 10 mg therapy, her SRED symptom resolved. The second case was a 70-year-old woman with RLS and sleep apnea. Soon after she was switched from zolpidem 10 mg to 12.5 mg of extended-release (ER) zolpidem, she developed amnesic SRED. After switching back to the immediate-release formulation of zolpidem, her nocturnal SRED resolved.

Dang *et al.* [14] reported the case of a 45-year-old man who was prescribed zolpidem and exhibited unexpected and bizarre eating behaviors during the somnambulistic state. After zolpidem was stopped, his SRED episodes were resolved.

Yun *et al.* [15] reported the case of a 45-year-old man with RLS and zolpidem-induced SRED. After zolpidem discontinuation, SRED did not recur. His RLS and related insomnia were controlled with pramipexole 0.5 mg and clonazepam 0.25 mg.

Hoque *et al.* [16] reported the case of a 51-year-old woman with zolpidem-induced SRED. A few weeks after starting zolpidem 10 mg, she started sleep walking and eating. She also experienced one episode of sleep driving. After zolpidem was stopped, all sleep-related symptoms immediately ceased and did not recur.

Wing *et al.* [17] reported the cases of eight patients (five females) who presented with SRED while taking 10 mg of zolpidem. The patients were reported to consume carbohydrates after a period of sleep. Six patients had comorbid OSA, for which one patient was already receiving continuous positive airway pressure (CPAP) treatment before the onset of SRED. None of the patients were diag-

nosed with RLS or periodic limb movement disorder.

Nzmalo *et al.* [18] reported the case of a 53-year-old woman with zolpidem-induced SRED. Her family witnessed several episodes of sleep eating, trying to drink various types of food, and sometimes cook during sleep. During these episodes, her eyes remained almost closed. However, she was unable to remember anything related to the episodes, and it was suggested to video record one of the episodes. Subsequently, zolpidem was stopped and the night eating episodes ceased.

Kim *et al.* [19] reported the case of a 57-year-old woman with RLS. She had been receiving zolpidem 10 mg daily for 6 months. During the treatment period, she ate forcefully without feeling hungry. Whenever her family members intervened during the eating episodes, she became angry and irritated. However, she could not recall her actions. Compulsive eating behavior disappeared after zolpidem administration was stopped.

Park *et al.* [8] reported the case of a 71-year-old man with SRED and complex behavior with anterograde amnesia. He had received 12.5 mg of controlled-release zolpidem. He also suffered from RLS and OSA. His SRED disappeared immediately after zolpidem discontinuation.

4. Discussion

In this article, we present 22 cases of zolpidem-induced SRED. SRED is characterized by recurrent episodes of involuntary eating and drinking during arousals from sleep with problematic consequences. However, there was no study that investigated the prevalence of zolpidem-induced SRED. Moreover, the mechanism underlying the association between zolpidem and SRED remain unclear. It has been suggested that diffuse cortical binding of zolpidem might trigger central pattern generators causing emergence of conserved primitive patterns such as walking and eating. These primitive patterns could indeed be potentiated by the sedation-amnestic properties of zolpidem [16]. Some possible risk factors have been hypothesized, including zolpidem dosage, sex, drug-drug interaction with serotonin reuptake inhibitors, protein-binding competition, body weight, and a combination of past history of sleepwalking, medication increasing delta sleep, and a precipitating stimulus. Polypharmacy with concurrent medication was another risk for SRED. The uniqueness of zolpidem compared to other benzodiazepine and nonbenzodiazepine hypnotics with regard to precipitating SRED remains unclear. Further studies related to the pathophysiology of SRED are needed in the future. Zolpidem-induced SRED can usually be improved by discontinuing zolpidem.

To confirm a definite association between zolpidem and SRED, resolution of SRED on stopping zolpidem should be shown. Given that differences as small as formulation could affect the likelihood of SRED, it is practical for clinicians to keep in mind that SRED may be observed with the use of particular agents or at particular dosages in some subjects. Future research will be required to deter-

mine whether it is possible to predict the pharmacologic profile that increases the risks of SRED related to zolpidem treatment 4.1.

5. Conclusion

Zolpidem is an effective hypnotic with a shorter half-life than other benzodiazepines. Zolpidem is widely prescribed owing to its favorable pharmacological properties for insomnia treatment. Clinicians should be aware of the unwarranted effects of zolpidem, provide appropriate management, and warn patients about the side effects of zolpidem use. Caution should be exercised while prescribing zolpidem to patients with insomnia. Future studies will be needed to reveal the relation between zolpidem and SRED.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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